postmortem microscopic examination of brain tissue. Yet, when it comes to detect the presence of the BSE agent in tissues this is determined by inoculating animals, usually mice, with material believed to be infected with BSE. Thus, there exists a need in the art to provide a means with which the agents responsible for the development of degenerative diseases of the nervous system, such as BSE, Creutzfeld Jacobs Disease ("CJD"), variant CJD ("vCJD") or transmissible spongiform encephalopathy ("TSE") related diseases, like scrapie and others are detected.

The problem of the present invention therefore resides in providing means, which enable a veterinary and/or physician to specifically detect the presence of agents causing BSE, CJD, vCJD and/or TSE related diseases.

In the course of the extensive studies leading to the invention the present inventors have found that one of the conformational changes the PrP^{C} undergoes in its transformation to PrP^{Sc} resides in a modification of the tertiary structure of the C-terminal region of PrP^{C}.

Thus, according to one embodiment, the present invention provides for an antibody directed to the C-terminal part of the PrP^{Sc} isoform or a part thereof, that is, to a three dimensional conformation of said part of the prion polypeptide exhibited in the "misfolded" form. Since the PrP^{C} form does exhibit a three dimensional conformation in this part of the prion polypeptide that is obviously different from PrP^{Sc}, the present antibodies are capable to selectively bind to the PrP^{Sc} isoform while not binding to the PrP^{C} form. They are therefore capable to distinguish between those isoforms.

The rejection of claim 1 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed.

It is the position of the U.S. Patent and Trademark Office ("PTO") that the limitation of a three dimensional structure, referred to in claim 1, is unclear. Applicant submits that the limitation "three dimensional conformation" as recited in claim 1 refers to a native (non-denatured) prion protein. The present application nowhere describes the prion protein as requiring a denaturing step in order for the antibody of claim 1 to bind to the three dimensional conformation of the prion protein. Therefore, it follows that the limitation refers to the native protein. Furthermore, it is taught in the instant application that proteinase K treatment is <u>not</u> required for the recognition of the PrP^{Sc} protein by the antibody of the present invention, because the recited antibody can distinguish between (i.e., selectively bind)

the PrP^{Sc} isoform but not the PrP^{C} isoform when both are in their native, three-dimensional conformation (see page 15, lines 22-30).

Therefore, applicant submits that the recitation of "three-dimensional conformation" in claim 1 would be understood by one skilled in the art as referring to a native, non-denatured prion protein. For these reasons, the rejection of claim 1 for indefiniteness should be withdrawn.

The rejection of claim 5 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed.

The PTO has asked for clarification of the limitation "linked to a marker" in claim 5. "Linked" as used in the present invention has the normal meaning of "bonded to" ("link . . .a connecting element, a tie or bond," see The American Heritage College Dictionary, 3d ed., pg. 789, Houghton Mifflin, NY (1993), attached herein as Exhibit 1). Applicant submits that this would be understood by one of ordinary skill in the art as referring to a chemical "bond" between the marker and the antibody, so that a second antibody (that itself may be linked to a marker) should not be comprised. In addition, the application discloses examples of markers which may be linked to the antibody of the present invention, including radioactive labels, fluorescent labels, or dyes (see page 7, lines 27-28). Such markers and their attachment to proteins, including to antibodies, are widely known and used in the art. Therefore, applicant submits that the meaning of "linked to a marker" in claim 5 is definite. Thus, the rejection of claim 5 for indefiniteness is improper and should be withdrawn.

The rejection of claims 6 and 14 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed.

The specific hybridoma cell line, CNCM-I-2476, that can be used to practice the present invention was deposited under the Budapest Treaty at the Collection Nationale de Cultures de Microorganisms, Institute Pasteur, and received a registration number on 10 May 2000, as disclosed in the instant application (see page 7, lines 28-30; page 11, lines 9-11; page 14, lines 2-3). A copy of the registration for deposit is attached herein as Exhibit 2. In view of the prior deposit under the Budapest Treaty, applicant's undersigned attorney asserts that hybridoma cell line CNCM-I-2476 will be irrevocably and without restriction made available to the public upon issuance of the patent. For this reason the rejection of claims 6 and 14 for lack of enablement is improper and should be withdrawn.

The rejection of claims 1-5, 12, 13, and 20 under 35 U.S.C. § 112 (1st para.) for lack of enablement is respectfully traversed.

It is the position of the PTO that the specification is not enabling for any antibodies other than the monoclonal antibody produced by the hybridoma CNCM-I-2476 disclosed in the present invention. The PTO cites U.S. Patent No. 5,773,572 to Fishleigh et al. ("Fishleigh") to support this position.

As noted above, the antibodies of the present invention became possible because applicant determined that in the PrP^{Sc} isoform, the C-terminus exhibits a different three-dimensional structure as compared to the "normal" PrP^{C} polypeptide, which different three dimensional structure results (phenotypically) in the clinical signs of mad cow disease (even though it is still the same protein having the same primary structure). Although PrP exhibits a low antigenicity, others showed it was possible to produce antibodies against both isoforms of prion protein (see, e.g., Fishleigh at col. 20, lines 55-60). Yet, the inherent low antigenicity of the polypeptide made it difficult to produce antibodies capable of distinguishing between the native, or non-denatured, PrP^{C} and PrP^{Sc} isoforms. The present invention teaches that antibodies capable of binding to the critical three dimensional "misfolded" structure of the PrP^{Sc} can be obtained by selecting a fragment of the C-terminus of the primary structure of the prion polypeptide and then proceeding as taught in the specification. As a result, other antibodies will be arrived at that are capable of distinguishing between PrP^{C} and PrP^{Sc}.

Therefore, applicant submits that by reading and carrying out the present invention as disclosed, an individual skilled in the art would be fully able to make additional antibodies capable of selectively binding to a three dimensional conformation provided by the C-terminal part of the PrP^{Sc} isoform of the prion protein or a portion thereof, without binding to the PrP^{C} form. Thus, the rejection of claims 1-5, 12, 13, and 20 for lack of enablement is improper and should be withdrawn.

The rejection of claims 1, 3-5, 13, and 20 under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,261,790 to O'Rourke ("O'Rourke") is respectfully traversed.

O'Rourke discloses monoclonal antibodies that specifically bind a conserved epitope of prion proteins, and the use of such antibodies to detect PrP^{Sc} in fixed or unfixed tissue that has been treated to unmask the PrP^{Sc} epitope and eliminate the availability of a corresponding epitope of PrP^{C} (see Abstract and Claim 1, col. 17). Due to the fact that PrP^{C}

is less resistant to exogenous influences such as proteinase K treatment or, as used in O'Rourke, heat treatment, only the PrP^{Sc} isoform survives the treatment and is detected with the antibody. The need for a denaturing treatment, such as applying heat to a sample prior to antibody detection, as required by O'Rourke, shows that the antibody of O'Rourke is clearly not capable of selectively distinguishing between the PrP^{C} and PrP^{Sc} isoforms in a sample. The antibodies provided in O'Rourke do not recognize the biologically relevant conformational distinctions between the normal and disease isoforms, as shown by the fact that O'Rourke's antibody requires the PrP^{Sc} first be "unmasked" and all potentially competing PrP^{C} has to be eliminated before the antibody can recognize the PrP^{Sc} isoform.

In contrast, claim 1 of the present invention is drawn to an antibody capable of selectively binding to a three dimensional conformation provided by the C-terminal part of the PrP^{Sc} isoform of the prion protein or a portion thereof, while not binding to the PrP^{C} form. The antibody of the present invention does not require "unmasking" of the PrP^{Sc} epitope, or elimination of PrP^{C} proteins in the sample to effect antibody binding (see Example 4). O'Rourke does not teach or claim the PrP^{Sc}-specific antibody of the present invention which does not bind to the PrP^{C} isoform of the prion protein. Thus, O'Rourke fails to teach or suggest each and every limitation of claim 1 and O'Rourke cannot anticipate claim 1 let alone claims 3-5, 13, and 20 dependent thereon. Therefore, the rejection of claims 1, 3-5, 13, and 20 under 35 U.S.C. § 102(e) as anticipated by O'Rourke is improper and should be withdrawn.

The rejection of claims 1, 2, 4, 5, 12, 13, and 20 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,846,533 to Prusiner et al. ("Prusiner") is respectfully traversed.

Prusiner describes the production of antibodies capable of binding to PrP^{Sc} *in situ*. However, these antibodies cannot distinguish between PrP^{Sc} and PrP^{C} *in situ* except by treating the composition containing PrP^{C} and/or PrP^{Sc} with proteinase K (see col. 4, lines 43-46). In contrast, the specificity of the anti- PrP^{Sc} antibodies of the present invention is such that treatment of the sample is not required for the antibody to distinguish between the PrP^{Sc} and PrP^{C} isoforms (see Example 4).

Furthermore, it is the position of the PTO that Figures 9, 11, and 12 of Prusiner are indicative of antibodies that bind to the native PrP^{Sc} while not binding to the normal PrP^{C} protein. Applicant submits that while Figures 9, 11, and 12 show binding of Prusiner's anti-PrP^{Sc} antibodies to the proteinase K core of PrP^{Sc}, ("SHa 27-30"), neither

these figures, nor any others in Prusiner, teach that these antibodies are not capable of binding to the PrP^C protein. Such a showing could have been made with a competitive binding assay, or controls in the ELISA or Western blots assays using a PrP^C protein in addition to the PrP^{Sc} prion protein fragment. Prusiner provides no such data. Absent such data, an antibody that selectively binds to the PrP^{Sc} isoform of the prion protein or a part thereof, but does not bind to the PrP^C form, has not been disclosed. Therefore, Prusiner fails to teach or suggest each and every element of the presently claimed invention and Prusiner cannot anticipate the antibody of claim 1 of the present invention let alone claims 2, 4, 5, 12, 13, and 20 dependent thereon. Thus, the rejection of claims 1, 2, 4, 5, 12, 13, and 20 under 35 U.S.C. § 102 (b) is improper and should be withdrawn.

In view of all of the foregoing, applicant submits that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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July 23, 2002 Date	JoAnn Whalen